REMARKS

Entry of the foregoing and further and favorable consideration of the subject application are respectfully requested.

As correctly stated in the Official Action, Claims 10, 11, and 13-31 are pending. Claims 20-24 stand withdrawn from consideration. Claims 10, 11, 13-19, and 25-31 stand rejected.

By the present amendment, Claims 25 and 26 have been canceled, without prejudice to or disclaimer of the subject matter contained therein. Applicants expressly reserve the right to file a continuation or divisional application on any subject matter canceled by the present amendment. Support for the amendment to Claims 10, 13, and 27 can be found, at least, on page 25, lines 22-24, and page 26, line 25 to page 28, line 1 of the present specification. The amendment to Claims 16 to 19, can be found, at least, on page 13, line 20 to page 16, line 23. Support for the amendment to Claim 27 can be found, at least, in Claim 24 as originally filed and page 25, lines 14-21 of the present specification. New Claims 32-36 are supported by, at least, page 8, lines 19-24 of the present specification. No new matter has been added.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 10-11, 13-19, and 25-31 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claims 10, 25, and 27 stand rejected as it is allegedly not clear how a compound can comprise anything other than itself. Claim 25 has been canceled, thereby mooting this

rejection as it applies to this claim. Without conceding to the merits of this rejection, and solely in an effort to expedite prosecution, by the present amendment, Claim 10 has been amended to recite a polypeptide fragment of a cathepsin L type cysteine protease present in healthy stratum corneum. Claim 27 has been amended to recite a monoclonal antibody or antisera to a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof.

Claims 10, 13, 25, and 27 stand rejected as allegedly awkward in the recitation of "polypeptide" and "protease" together and for the recitation of "natural" and "synthetic" polypeptide. Claim 25 has been canceled, thereby mooting this rejection as it applies to this claim. Applicants respectfully submit that the present claim language is clear in referring to the polypeptide as being a cysteine protease. Nevertheless, without conceding to the merits of this rejection and solely in an effort to expedite prosecution, the rejected claims have been amended to clearly recite a cathepsin L type cysteine protease or a polypeptide fragment thereof. Additionally, "natural" and "synthetic" have been deleted from the claims, thereby mooting this rejection.

Claims 10, 13, and 27 stand rejected for the recitation of a molecular weight range but without indicating the means by which the molecular weight was determined. Additionally, the Examiner asserts that the range of molecular weight is broad compared to any known method of determining molecular weight. Claim 25 has been canceled, thereby mooting this rejection as it applies to this claim. This rejection is respectfully traversed.

The rejected claims recite an "apparent molecular weight," which is explicitly defined in the specification on page 8, lines 3-14, as:

> the molecular weight obtained for the polypeptide by comparing its electrophoretic mobility with those of standard proteins of known molecular weights on a polyacrylamide/sodium dodecyl sulfate gel, or alternatively, by comparing the elution volume of the polypeptide with that of standard proteins of known molecular weights in exclusion chromatography (according to the techniques described in "Protein Purification," J-C Janson and L. Ryden, VCH Publisher Inc., N.Y., 1989).

In view of this definition, Applicants submit that the recitation of "apparent molecular weight" without reference to a method of determination is not indefinite. Moreover, Applicants note that this same claim language was allowed by the current Examiner in the parent case, now issued U.S. Patent No. 6,274,364.

With regard to the molecular weight range, the Examiner appears to have misunderstood the scope of the rejected claims. The claims are not directed to a single protease polypeptide fragment, but to any protease polypeptide fragment having the recited characteristics. While a mass range of 15 to 32 kilodaltons for a single protein would admittedly be a large range, Applicants submit that this range is not *per se* incredible when applied to a group of cathepsin L type cysteine proteases, which may be from different organisms with varying homology in structure. Moreover, various size fragments may be produced when proteolysis of the parent cysteine protease occurs. Withdrawal of this rejection is respectfully requested.

Claim 10 stands rejected as indefinite in the recitation of a "polypeptide fragment." The Examiner asserts that the parent of the polypeptide fragment is unclear. This rejection is respectfully traversed.

By the present amendment, Claim 10 refers to a polypeptide fragment of a cathepsin L type cysteine protease present in healthy stratum corneum having an apparent molecular weight ranging from 15 to 32 kilodaltons. Applicants respectfully submit that the specification makes clear that while the parent cysteine protease can be isolated, polypeptide fragments of this parent cysteine protease can also be obtained, *e.g.*, by proteolysis. *See* page 11, lines 9-11 of the specification. Moreover, the polypeptide fragments obtained may be even more active than the parent cysteine protease. *See* page 13, line 20 to page 16, line 23 (discussing effects of urea and protease activators on other cathepsins). Applicants respectfully submit that the meaning of a polypeptide fragment of a cathepsin L type cysteine protease as recited in the present claims is clear. Withdrawal of this rejection is respectfully requested.

Claim 25 stands rejected as being inconsistent in referring to a polypeptide cathepsin L type protease and a "complex." Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, Claim 25 has been canceled, thereby mooting this rejection.

Claim 27 stands rejected as confusing as to whether it is an antibody or a polypeptide of a cathepsin L type cysteine protease. Without conceding to the merits of

this rejection and solely in an effort to expedite prosecution, Claim 27 has been amended to recite a monoclonal antibody or antisera to the cysteine protease polypeptide or fragment thereof. Withdrawal of this rejection is respectfully requested.

The Examiner further states on page 4 of the Official Action that it is unclear what is being claimed. By the present amendment, Applicants respectfully submit that the present invention is clearly claimed. Claims 10 and 11 are directed to a polypeptide fragment of a cathepsin L type cysteine protease present in healthy stratum corneum. Claims 13-19 and 28-31 are directed to a cosmetic or pharmaceutical composition comprising the cathepsin L type cysteine protease present in healthy stratum corneum, or a polypeptide fragment thereof (*e.g.*, that of Claims 10 and 11). Claim 27 is directed to a monoclonal antibody or antisera to the cathepsin L type cysteine protease present in healthy stratum corneum or polypeptide fragment thereof.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 10-11, 13-19, and 25-31 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. The Examiner asserts that the specification is enabling for a specific cysteine protease, G4, but does not reasonably provide enablement for fragments thereof. The Examiner argues that the specification does not provide disclosure of a polypeptide fragment having cathepsin L type cysteine protease activity or for synthetic polypeptides. Claim 25 has been canceled by the present amendment, thereby

mooting this rejection as it applies to this claim. This rejection, to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Applicants respectfully submit that the specification **does** provide adequate enablement for fragments of the cysteine protease. The specification need not teach, and preferably does not, that which is known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Proteolysis is a standard technique known in the art and occurs naturally *in vivo*. Various proteolytic enzymes are known and used routinely. Moreover, the testing for activity of cathepsin L type cysteine proteases is also known in the art and is described in the instant specification on page 32-33. The art and the specification also disclose various enzyme assays to distinguish cathepsin L type cysteine proteases from other types of proteases. Accordingly, one skilled in the art is well-equipped to readily determine whether a polypeptide fragment of a cathepsin L type cysteine protease present in healthy stratum corneum is also active as a cathepsin L type cysteine protease, as this merely requires routine experimentation. Disclosure of specific residues is not required to enable the presently claimed invention, as one can readily isolate and test the activity of fragments without such knowledge. Applicants further point out that the publications cited by the Examiner in connection with the rejection of claims under 35 U.S.C. § 102 also supports the fact that the presently claimed invention is enabled. For instance, the Kawada et al., Mason et al., and Baricos et al. publications describe fragmentation of a parent cathepsin L protease. While Applicants have identified a different cathepsin L type protease; (discussed in further detail below) these publications demonstrate the one skilled

in the art can readily identify fragments and their commensurate activity. Withdrawal of this rejection is respectfully requested.

By the present amendment, the recitation of "synthetic polypeptide" has been deleted from the present claims, thereby mooting this rejection.

Claims 16-19 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling for any protease activator. This rejection, to the extent that it may apply to the claims, as amended, is respectfully traversed.

Applicants respectfully submit that the specification does provide enablement for various protease activators. The Examiner admits that the specification provides support for glycerol, EDTA, and reducing agents. Moreover, urea is specifically described on page 14, as known to increase the activity of other cathepsins, particularly cathepsin L and D, and therefore can be considered to be a protease activator of cathepsin L. Glycerol, EDTA, reducing agents, and transglutaminase are specifically discussed as to enhancing the activity of cysteine proteases through various mechanisms and can thus be described as protease activators. The Examiner appears to contend that the language "protease activator" is inconsistent with the art-accepted meaning of this phrase. While Applicants disagree that the use of this term is inconsistent with art-accepted use, by the present amendment, "protease activator" has been deleted from the claims and "protease activity enhancer" has been added instead. Such a recitation is adequately supported by the specification, page 13, line 20, to page 16, line 23, which discusses a number of compounds that enhance the activity of proteases, particularly those in the skin. However,

Applicants are willing to entertain any alternative claim language the Examiner cares to suggest. Further, Applicants respectfully submit that one skilled in the art can readily determine if a substance enhances the activity of the cathepsin L type cysteine protease or polypeptide fragment thereof using standard assay techniques such as those described in the Examples of the present specification. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 10-11, 13-15, 25, and 27 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Kawada et al. (1997). The Examiner argues that Kawada et al. disclose the isolation and characterization of human cathepsin L protease from psoriatic epidermis. Claim 25 has been canceled, thereby mooting this rejection as it applies to this claim. This rejection, to the extent that it may apply to the remaining claims as amended is respectfully requested.

By the present amendment, the present claims are directed to a cathepsin L type cysteine protease present in healthy stratum corneum (Claims 13 and 27)and polypeptide fragments thereof (Claims 10, 13, and 27). Kawada et al. relates to cathepsins L, B, and D. Cathepsin L is reported by Kawada et al. to be absent from the cornified layer of the skin. Specifically, at page 90, left column, lines 8-9, Kawada et al. state that, "no immunoreactivity for cathepsin L, B, or D was shown in the cornified layer." Thus, the cathepsin L disclosed by Kawada et al. is outside of the scope of the present claims, and Kawada et al. therefore cannot anticipate the present claims. Additionally, with regard to

Claims 13-15, Kawada et al. do not disclose a cosmetic or pharmaceutical composition comprising the cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof formulated into a physiological acceptable medium. With regard to Claim 27, Kawada et al. do not disclose a monoclonal antibody or antisera to a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. Withdrawal of this rejection is respectfully requested.

Claims 10-11, 13-15, 25, and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Rao et al. (1995). The Examiner asserts that Rao et al. disclose cathepsin L from human gliomas having a mass of about 29 kDa. Claim 25 has been canceled by the present amendment, thereby mooting this rejection. This rejection, to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Rao et al. fail to disclose a cysteine protease, or a polypeptide fragment thereof, present in healthy stratum corneum. The cathepsin L enzyme by Rao et al. is present in normal brain and tumor tissue. Applicants respectfully submit that there is no reason to conclude that this enzyme is inherently the same enzyme as that claimed by Applicants that is present in the stratum corneum. In fact, the disclosure of Kawada et al. suggests the contrary in stating that cathepsin L is not found in the cornified layer. In order to anticipate a claim under 35 U.S.C. § 102, a publication must disclose or suggest every limitation of the claimed invention. There is simply no disclosure in Rao et al. of a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. Additionally, with regard to claim 13-15, Rao et al. do not disclose a

cosmetic or pharmaceutical composition comprising the cathepsin L type cysteine protease present in healthy stratum corneum or polypeptide fragment thereof formulated into a physiological acceptable medium. With regard to Claim 27, Rao et al. do not disclose a monoclonal antibody or antisera to a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. Withdrawal of this rejection is respectfully requested.

Claims 10-11, 13-19, 25, and 27 stand rejected under 35 U.S.C. § 102, as allegedly anticipated by Reilly et al. (1989) and Claims 10-11, 13-15, 25, and 27, as allegedly anticipated by Reilly et al. (1990). The Examiner argues that Reilly et al. disclose cathepsin L from human alveolar macrophages. Claim 25 has been canceled by the present amendment, thereby mooting this rejection as it applies to this claim. This rejection, to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Applicants respectfully submit that upon review of the reference, specifically at page 495, Col. 1, of Reilly 1989, it is clear that the enzyme reported by Reilly is the same one that was previously isolated by Gal and Gottesman. *See*, *e.g.*, the sentence bridging pages 492-493, wherein the authors note that immunoreaction with an antibody specific to human liver cathepsin A showed that the cathepsin L derived from human macrophages had the same molecular weight as the previously purified cathepsin L enzyme. The Examiner's attention is directed to the first sentence in the Abstract which describes that the cathepsin L of the reference, which was partially purified from lysates of freshly isolated macrophages (from lungs of apparently healthy adults) was found to be

chromatographically and catalytically identical with liver cathepsin L. (*See* page 495, left-hand column, of Reilly et al. 1989).

Moreover, the later Reilly et al. (1990) reference similarly relates to the same cathepsin L enzyme described in the previous Reilly reference. As noted above, and supported by Reilly (1989), this is the same cathespin L enzyme previously isolated by Gal and Gottesman (1989), a copy of which reference is attached to this Reply as Annex 7.

However, this enzyme is not the same cysteine protease isolated by Applicants. In order to substantiate this difference, the present Applicants obtained the human cathepsin L of the reference (Gal and Gottesman) from a supplier of this enzyme ICN (Annex 1 to this Response comprises a copy of the ICN Catalog identifying this enzyme.) This enzyme is also described in Annex 6 to this Response, which shows the enzymatic activity of this enzyme (referred therein as HCP).

In particular, various comparisons were made in order to demonstrate that the enzyme of the present invention is not equivalent to that of the reference. For example, the isoelectric point of the enzyme of the invention *vis-a-vis* the cited publications (Reilly references) were compared. The Examiner is respectfully referred to Annex 2 and Annex 3 attached to this Reply, which indicate that the enzyme of the prior art, *i.*e., human cathepsin L possesses an acidic isoelectric point ranging from about 4 to 5. By contrast, the isoelectric point of the subject enzyme, as described in the present application, is slightly acidic to basic and ranges from 6 to 9. The isoelectric point of the subject enzyme finds support, *e.g.*,. in original Claim 2, and page 28 of the subject application. Therefore,

it is clear based on this significant difference in isoelectric points that the enzyme of the reference does not correspond to that of the present invention.

Moreover, a comparative test was effected in order to compare the ability of the enzyme of the present invention to digest a substrate in the presence or absence of an HCL specific antibody. The results of this assay are contained in Annex 4 attached to this Reply. In this assay, SCP and HCL were prepared by HPLC under the same conditions (column type: HR10/30 from Pharmacia Biotech using an injection volume of 250 μl on a Biorad apparatus).

In this test, acetonic powder obtained from stratum corneum was diluted in a chromatographic buffer (phosphate buffer, 50 mM pH 7, NaCl 0.015M, Triton X-100, 0.1%) resulting in a solution have a total protein concentration of 0.12 mg/ml. Also, HCL obtained from ICN (the enzyme of Gal and Gottesman) was prepared using the same buffer to obtain a protein concentration of 0.1 μg for each injected 250 μl. Dosages were performed using 10 μl of protein-containing fractions having a molecular weight ranging from 70 kD to 15 kD.

A non-specific substrate test was then effected using 200 μl of ENZCHEK substrate (Molecular Probes Kit No. E6638) contained in a buffer (0.1M pH 5 acetate buffer, 5 mM EDTA, 5 mM cysteine, 0.1% Triton X-100) which were then added to each 10 μl fraction. Also, a specific substrate test was effected using 10 μM of a Z (Phe-Arg)$_2$R110 peptide (specific substrate of L cathepsin) which were added to each 10 μl fraction. Tests were performed before or after immunoprecipitation of the peptide with a L cathepsin-specific antibody (anti-human cathepsin L polyclonal antibody, obtained from Biogenesis Catalog

No. 1911-0507, at 2.6 mg/ml of IgG) using a Roche molecular kit termed "G protein immunoprecipitation kit," having an antibody concentration of 20 μl/ml of protein in solution.

Activities were measured by monitoring the fluorescence produced by the degradation products from the substrates. Fluorescence was measured using a Molecular Dynamics Biolumin apparatus with λex equaling 535, and λem equaling 485. The results of these fluorescence comparisons are contained in Figures 1 and 2 of Annex 5. Figure 1 contains the results obtained using SCP, the enzyme of the invention on ENZCHEK and R110 substrates in the presence or absence of antibodies (anticat L).

Figure 2 contains the results obtained with HCL (enzyme of prior art), on ENZCHEK and R110 substrates in the presence or absence of antibodies (anti-cat L). It can be clearly seen from the results in the Figures that the antibodies to anti-HCL immunoprecipitated the activity of HCL. By contrast, this antibody did not have any effect on the activity of SCP (because it does not recognize this polypeptide). Moreover, it can seen that the molecular weights of these two polypeptides are different as they eluted in different fractions, as shown by the results contained in Figures 1 and 2. Still further, SCP exhibited substrate specificity with ENZCHEK as shown in Figure 1. By contrast, the HCL enzyme exhibited no fluorescence with ENZCHEK (see Figure 2).

Thus, based on this comparison, *i.e.*, the difference of these enzymes to digest specific peptide substrates, and further the significance difference in isoelectric points and finally based on the difference in immunoreactivities, it is clear that the enzyme of Reilly (1989) (which actually corresponds to the enzyme of Gal and Gottesman) (Annex 7) is not

equivalent to the enzyme of the present invention. This data was previously presented in the parent case of the present application. Applicants express their willingness to submit this data in declaration form if the Examiner deems it necessary.

Reilly et al. (both 1989 and 1990) do not disclose a cathepsin L type cysteine protease present in healthy stratum corneum, or a polypeptide fragment thereof. The cathepsin L enzyme of Reilly et al. is present in human alveolar macrophages. Applicants respectfully submit that there is no reason to conclude that this enzyme is inherently the same enzyme as that claimed by Applicants that is present in the stratum corneum. In fact, the data discussed above and the disclosure of Kawada et al., which states that cathepsin L is not found in the cornified layer, suggest otherwise. In order to anticipate a claim under 35 U.S.C. § 102, a publication must disclose or suggest every limitation of the claimed invention. There is simply no disclosure in Reilly et al. of a cathepsin L type cysteine protease in healthy stratum corneum or a polypeptide fragment thereof. With regard to Claim 27, Reilly et al. do not disclose a monoclonal antibody or antisera to a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment. Withdrawal of this rejection is respectfully requested.

Claims 10-11, 13-15, 25, and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mason et al. (1984) and Claims 10-11, 13-19, 25, and 27 as allegedly anticipated by Mason et al. (1985). The Examiner asserts that Mason et al. disclose cathepsin L from human liver. Claim 25 has been canceled by the present

amendment, thereby mooting this rejection as it applies to this claim. This rejection to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Applicants respectfully submit that it is clear upon review of Gal and Gottesman, at page 304, right-hand column, that the HCP of Gal and Gottesman is the same enzyme reported by Mason et al. Therefore, based on the above-discussed comparison, it is not equivalent to the enzyme of the present invention.

Mason et al. do not disclose a cathepsin L type cysteine protease present in healthy stratum corneum, or a polypeptide fragment thereof. The cathepsin L enzyme by Mason et al. is present in liver. Applicants respectfully submit that there is no reason to conclude that this enzyme is inherently the same enzyme as that claimed by Applicants that is present in the stratum corneum. In fact, the data presented above and the disclosure of Kawada et al., which states that cathepsin L is not found in the cornified layer, suggest the contrary. In order to anticipate a claim under 35 U.S.C. § 102, a publication must disclose or suggest every limitation of the claimed invention. There is simply no disclosure in Mason et al. of a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. Additionally, with regard to Claims 13-15, Mason et al. do not disclose a cosmetic or pharmaceutical composition comprising the cathepsin L type cysteine protease present in healthy stratum corneum or polypeptide fragment thereof formulated into a physiological acceptable medium. With regard to Claim 27, Mason et al. do not disclose a monoclonal antibody or antisera to a cathepsin L type cysteine protease present in healthy stratum corneum or polypeptide fragment thereof. Withdrawal of this rejection is respectfully requested.

Claims 10-11, 13-19, 25, and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Baricos et al. (1988). The Examiner argues that Baricos et al. disclose cathepsin L from kidney. Claim 25 has been canceled by the present amendment, thereby mooting this rejection as it applies to this claim. This rejection, to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Applicants respectfully submit that the enzyme of Baricos et al. also is the same enzyme described by Mason et al., which in turn is the same enzyme reported by Gal and Gottesman. The fact that this enzyme corresponds to that of Gal and Gottesman can be appreciated based on the disclosure at page 301, wherein the authors teach that the described cathepsin L was purified "essentially as described by Mason et al. (1985)." Therefore, the human cathepsin described by Baricos corresponds to that of Gal and Gottesman, which is distinguishable from that of the present invention.

Baricos et al. do not disclose a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. The cathepsin L enzyme by Baricos et al. is present in kidney. Applicants respectfully submit that there is no reason to conclude that this enzyme is inherently the same enzyme as that claimed by Applicants that is present in the stratum corneum. In fact, the data presented above and the disclsoure of Kawada et al., which states that cathepsin L is not found in stratum corneum, suggest otherwise. In order to anticipate a claim under 35 U.S.C. § 102, a publication must disclose or suggest every limitation of the claimed invention. There is simply no disclosure in Baricos et al. of a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. Additionally, with regard to Claims 13-15, Baricos et al. do not disclose

a cosmetic or pharmaceutical composition comprising a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof formulated into a physiological acceptable medium. With regard to Claim 27, Baricos et al. do not disclose a monoclonal antibody or antisera to a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. Withdrawal of this rejection is respectfully requested.

Claims 10-11, 13-15, 25, and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chauhan et al. (1993). The Examiner asserts that Chauhan et al. disclose a human cathepsin L gene from cervical cancer, liver, and kidney cells. Claim 25 has been canceled by the present amendment, thereby mooting this rejection as it applies to this claim. This rejection, to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Applicants respectfully point out that the presently claimed invention is not directed to a gene or DNA sequence but rather a cathepsin L cysteine protease present in healthy stratum corneum, polypeptide fragments thereof, compositions containing such, and monoclonal antibodies or antisera to such polypeptides and fragments. Chauhan et al. describe the genomic organization of the cathepsin L gene, wherein the described cDNAs correspond to the cathepsin L of Gal and Gottesman. The fact that Chauhan et al. refer to a cDNA encoding the enzyme of Gal and Gottesman is clear based on page 1039, right-hand column, of the reference, wherein they describe that the cDNAs that they expressed are encoded by a single gene and correspond to their previously isolated enzyme.

Applicants note also that the previous isolated enzyme is that of Gal and Gottesman, which paper is cited as reference 9 in this document. Therefore, similarly, this reference also fails to teach or suggest the specific enzyme of the claimed invention. In particular, the differences between the enzyme encoded by the disclosed cDNA and that of the present invention is clear based on the comparative data already discussed. Therefore, Chauhan et al. cannot anticipate the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Claims 10-11, 13-15, 25, and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Uchiumi et al. (JP 06192124). The Examiner argues that Uchiumi allegedly disclose a precursor form of cathpsin L derived from human fibroblasts. This precursor has an apparent molecular weight of 37 $\pm$ 3. Claim 25 has been canceled by the present amendment, thereby mooting this rejection as it applies to this claim. This rejection, to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Similar to the previous references, this document likewise pertains to the human cathepsin L disclosed by Gal and Gottesman which, for the reasons set forth above, is distinguishable from the enzyme of the present invention. This fact is supported by Annex 8 to this Reply, which contains an English translation of paragraphs 12 and 13 of this document. It is apparent from these translated paragraphs that the cathepsin L described by Uchiumi et al is the same enzyme described by Mason et al., which is in turn is the same enzyme disclosed by Gal and Gottesman which has been distinguished from the enzyme of

the present invention. In particular, kindly note the last paragraph of the letter of Kobayashi, wherein it is noted from the context of the above two paragraphs that the reference pertains to human cathepsin L, or its pre or pro form as are described by Mason et al. As discussed above, the enzyme of Mason et al. is the same enzyme reported by Gal and Gottesman which differs from that of the present invention.

Uchiumi et al. do not disclose a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. The cathepsin L enzyme by Uchiumi et al. is present in human fibroblasts. Applicants respectfully submit that there is no reason to conclude that this enzyme is inherently the same enzyme as that claimed by Applicants that is present in the stratum corneum. In fact, the data presented above and the disclosure of Kawada et al., which states that cathepsin L is not found in the cornified layer, suggest otherwise. In order to anticipate a claim under 35 U.S.C. § 102, a publication must disclose or suggest every limitation of the claimed invention. There is simply no disclosure in Uchiumi et al. of a cathepsin L type cysteine protease present in healthy stratum corneum or a polypeptide fragment thereof. Additionally, with regard to Claims 13-15, Uchiumi et al. do not disclose a cosmetic or pharmaceutical composition comprising a cathepsin L type cysteine protease present in healthy stratum corneum or polypeptide fragment thereof formulated into a physiological acceptable medium. With regard to Claim 27, Uchiumi et al. do not disclose a monoclonal antibody or antisera to a cathepsin L type cysteine protease present in healthy stratum corneum or polypeptide fragment thereof. Applicants point out that the present claims dictate an apparent molecular weight range of 15 to 32 kDa. The protein disclosed by Uchiumi et al. is at

least 34 kDa (37 $\pm$ 3). Accordingly, Uchiumi does not anticipate the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 10-11, 13-19, 25, and 27 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kawada et al. (1997), Rao et al. (1995), Mason et al. (1984), Mason et al. (1985), Baricos et al. (1988), Chauhan et al. (1993), and Uchiumi et al (JP 06192124). The Examiner argues that one skilled in the art would have been motivated to isolate a cathepsin L from human epidermis having a pI of 6-9, a mass of 25-30 kD and a pH optimum of 3.5-6.5 in view of the teachings of the cited publications because the reference suggest that there is only one cathepsin L in human tissues. Claim 25 has been canceled by the present amendment, thereby mooting this rejection as it applies to this claim. This rejection, to the extent that it may apply to the remaining claims, as amended, is respectfully traversed.

Deficiencies of all of the cited references have been discussed above. For the reasons set forth therein, and as substantiated by Annex 1 to 8 attached to this Reply, none of these references teaches or suggests a cathepsin L typecysteine protease having the specific characteristics of that of the presently claimed invention. Rather, most of these references pertain to a specific cysteine protease disclosed by Gal and Gottesman which is distinguishable from that of the present invention based on its isoelectric point, immunological properties, and proteolytic activity. Moreover, the enzyme of the other

reference, *i.e.*, Kawada et al, is distinguishable from the present invention in that it is not expressed in the stratum corneum, unlike the enzyme of the presently claimed invention.

Moreover, none of these references renders obvious the claimed invention as there would be no expectation that a distinct cysteine protease could be isolated from the stratum corneum having the specific properties of the present invention. Applicants respectfully submit that because a category of protein is found in some tissues, this is not motivation to search for similar proteins in other dissimilar tissues. The present claims are directed to a cathepsin L type cysteine protease present in healthy stratum corneum, polypeptide fragments thereof, cosmetic/pharmaceutical compositions containing such, and monoclonal antibodies or antiserum to such cathepsin L type cysteine proteases present in healthy stratum corneum and polypeptide fragments thereof. In fact, the disclosure of Kawada et al. explicitly teach away from searching for a cathepsin L type cysteine protease in healthy stratum corneum. As mentioned in the passage of Kawada et al. cited above, Kawada et al. explicitly state that a cathepsin L type cysteine protease (such as that disclosed by the presently claimed invention) was not found in the cornified. Thus, one skilled in the art would not be motivated to obtain an isolated cathepsin L-type cysteine protease from healthy stratum corneum. Additionally, as Applicants have demonstrated above, and during prosecution of the parent application, the cathepsin L type cysteine protease of the presently claimed invention is distinguishable from the cathepsin L cysteine proteases of the cited publications. Namely, the presently claimed cathepsin L type cysteine protease does not possess similar immunoreactivity (based on the findings of Kawada et al. and Applicants' own comparative data), has a different isoelectric point from, and has different

substrate activity than known human cathepsin L (*i.e.*, that of the Reilly et al. publications). Because none of the cited publications, either alone or in combination, disclose or suggest each and every claim limitation, and in fact teach away from the presently claimed invention, they cannot render the presently claimed invention obvious. Withdrawal of this rejection is respectfully requested.

Conclusions

From the foregoing, further and favorable consideration of the subject application are respectfully requested.

If there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone Applicants' undersigned representative so that prosecution may be expedited.

Respectfully submitted,

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Date: June 26, 2003

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Attachment to REPLY & AMENDMENT dated June 26, 2003

Mark-up of Claims

10. (Twice Amended) An isolated, substantially pure [natural or synthetic] polypeptide fragment [comprising] of a cathepsin L type cysteine protease present in healthy stratum corneum having an apparent molecular weight ranging from 15 to 32 kilodaltons;

wherein the [cysteine protease] polypeptide fragment [is a polypeptide fragment] has a cathepsin L type cysteine protease activity.

11. (Amended) The polypeptide fragment as defined by Claim 10, obtained via proteolysis of said cathepsin L type cysteine protease [polypeptide].

13. (Twice Amended) A cosmetic/pharmaceutical composition comprising an isolated, substantially pure [natural or synthetic polypeptide comprising a] cathepsin L type cysteine protease present in healthy stratum corneum having an apparent molecular weight ranging from 15 to 32 kilodaltons, or polypeptide fragment thereof having cathepsin L type cysteine protease activity;

formulated into physiologically acceptable medium therefor.

14. (Twice Amended) The cosmetic/pharmaceutical composition as defined by Claim 13, comprising from about 0.00001% to 50% by weight of said cathepsin L type cysteine protease [polypeptide] or polypeptide fragment thereof.

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15. (Amended) The cosmetic/pharmaceutical composition as defined by Claim 14, comprising from about 0.001% to 10% by weight of said cathepsin L type cysteine protease [polypeptide] or polypeptide fragment thereof.

16. (Amended) The cosmetic/pharmaceutical composition as defined by Claim 13, further comprising at least one [protease activator] protease activity enhancer.

17. (Amended) The cosmetic/pharmaceutical composition as defined by Claim 16, said at least one [protease activator] protease activity enhancer comprising glycerol, urea or derivative thereof, transglutaminase, EDTA, reducing agent, or combination thereof.

18. (Amended) The cosmetic/pharmaceutical composition as defined by Claim 16, comprising from about 0.00001% to 15% by weight of said at least one [protease activator] protease activity enhancer.

19. (Amended) The cosmetic/pharmaceutical composition as defined by Claim 18, comprising from about 0.0001% to 10% by weight of said at least one [protease activator] protease activity enhancer.

27. (Amended) [An isolated, substantially pure natural or synthetic polypeptide comprising] A monoclonal antibody or antisera to a cathepsin L type cysteine

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protease present in healthy stratum corneum having an apparent molecular weight ranging from 15 to 32 kilodaltons, or a polypeptide fragment thereof having cathepsin L type cysteine protease activity[;

wherein the cysteine protease polypeptide is a monoclonal antibody or antisera prepared/purified from the cysteine protease polypeptide, or polypeptide fragment thereof].